REMARKS

Applicants respectfully request entry of the amendment to paragraph [0001] of the specification to cancel some of the priority claims. No new matter has been added.

Applicants submit the enclosed drawings FIGS. 15-18, and amend paragraph [0153] of the specification as filed to recite FIGS. "15-18" instead of FIGS. "4-7." Support for these amendments are found at paragraph [0244] of the specification as filed and in FIGS. 4-7 of U.S. Application No. 10/763,498 (the "'498 application"), to which this application claims priority and incorporates by reference in its entirety at paragraph [0001] of the specification as filed. As required under 37 C.F.R. § 1.74, Applicants insert the brief descriptions of FIGS. 15-18 into the instant application after paragraph [0033] of the specification as filed. The brief descriptions are supported, for example, at paragraph [0244] of the specification as filed and at paragraphs [0034]-[0037] of the '498 application. Thus, no new matter has been added.

Claims 13, 15, 17, 18, 25, 26, 29, 30, 33-35, 43 and 47-69 are pending in the present application upon entry of this amendment. Claims 44-46 are canceled without prejudice and new claims 47-69 are added. Claims 13, 17, 18, 25, 29, 33 and 34 have been amended. Claims 44-46 have been canceled as drawn to a non-elected invention. Support for the amended and new claims can be found throughout the specification, such as described below. No new matter has been added.

Amended claims 13 and 25 are supported by Compound 7 in Scheme 1 at Page 82 of the specification and Compound S7 in Appendix A. Amended claim 34 is also supported by compound S7 in Appendix A. New claims 47-59 and 61-69 are supported as detailed above and by formula (g), embodiments thereof, and Compounds S20, S27, and S36 of Appendix A. Claims 44-69 read on the previously elected Group II and formula (g). The claims encompass elected species S36 when R_1 = OR', R' = methyl (an alkyl), R_2 and R_3 = H, and R_4 = carboxylic acid.

Priority

Applicants respectfully request entry of the amendment to the specification to cancel certain claims to priority. No new matter has been added. As indicated in the above amendment to the specification, Applicants wish to retain their claim to priority to U.S. Patent Application Serial No. 10/763,498, filed on January 22, 2004, now abandoned.

Applicants wish to note that U.S. Application No. 10/763,498, to which this application claims priority at paragraph [0001], has a filing date of 1/22/2004, not 3/25/2004 as recited at page 2 of the Office Action.

Specification

The Office Action states, "the description of the figures and the labels on the figures suggest [] testing was simply for JTV-519, not the compound S36," despite the statement in paragraph [0153] at page 63 of the specification as filed that "[a]s shown in FIGS. 4-7, for example, one of the inventors' compounds, S36, has hERG blocking activity that is approximately 5- to 10-fold lower than the hERG blocking activity of JTV-519." (Paragraph [0153] of the of the specification as filed corresponds to paragraph [0244] of the application as published).

As noted above, Applicants submit the attached drawings FIGS. 15-18, and amend paragraph [0153] of the specification as filed to recite FIGS. "15-18" instead of FIGS. "4-7."

FIGS. 16-18 show that S36 has hERG blocking activity that is approximately 5- to 10-fold lower than the hERG blocking activity of JTV-519. (S36 is referred to as "JTV-S36" in both FIGS. 16-18 and in the '498 application at FIGS. 4-7 and paragraphs [0035]-[0037].) Thus, Applicants believe that the objection has been overcome and respectfully request its withdrawal.

Rejections Under 35 U.S.C. § 112 First Paragraph

Claims 13, 15, 17, 18, 25, 26, 29, 30, 33-35, and 43 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabling a person skilled in the art to use the invention commensurate in scope with these claims. Applicants respectfully traverse the rejection.

The Office Action states at page 4 that the specification "does not reasonably provide enablement for a method for preventing a decrease in the level of RyR2-bound FKBP12.6 in a subject or preventing cardiac conditions generally." The Office Action states at page 5 that "[t]here is no clear evidence," "not sufficient guidance," and/or not sufficient "working examples" showing these results. Applicants respectfully disagree, however, solely to expedite prosecution, the applicants have amended claim 13 to delete the term "preventing".

The Office Action acknowledges that the specification is "enabling for increase[ing] the

binding of FKBP12.6 to RyR2 with S36 in a subject." Page 4, lines 6-7 of the Office Action. This is claimed specifically in dependent claim 26. Applicants note that S36 is an illustrative member of the genus of formula (g) that is disclosed in claim 13." Furthermore, Figure 12 and Example 13 demonstrate that illustrative compounds of the claimed formula (g), S7, S20, S27 and S36, increase the binding of FKBP12.6 to RyR2 *in vitro*. To further support the claims, Applicants submit the attached Appendix B showing that compounds of claimed formula (g), including MolID Nos. 7, 27, 38, 58, 77, and 109, increase the binding of FKBP12.6 to RyR2. Increased FKBP12.6 binding to RyR2 is shown by either the EC50 of the compounds or their activity at 100 nM in an *in vitro* assay for FKBP12.6 binding to RyR2 (where Y means the tested compound caused increased FKBP12.6 binding to RyR2). Thus, illustrative compounds of the claimed formula (g) increase FKBP12.6 binding to RyR2, and methods of increasing the binding of FKBP12.6 to RyR2 that comprise administering compounds of the claimed formula (g) are enabled by the disclosure.

Thus, Applicants believe that the rejection of claim 13 and its dependent claims 15, 17, 18, 25, and 47-52 under 35 U.S.C. § 112, first paragraph has been overcome, and respectfully request its withdrawal.

The Office Action states, "The specification merely states that S36 prevents cardiac arrhythmias in FKBP12.6+/- mice," but acknowledges that the specification provides evidence that S36 prevents cardiac arrhythmias. Page 4, last two lines to Page 5, line 2 of the Office Action ("There is no clear evidence showing that S36 … prevents cardiac conditions other than cardiac arrhythmias"); See e.g., FIG. 13. New dependent claim 62 claims this subject matter, and depends from new independent claim 59. S36 is an illustrative member of formula (g) claimed in claim 59. Applicants also note that experimental data for even one species can support patentability of an encompassing genus. Thus, Applicants believe that claims 59 and its dependent claims, including claim 62, are patentable.

I recommend deleting this passage. We are not claiming that compounds a-h prevent cardiac conditions. We are arguing that compound (g) prevents cardiac arrhythmia, and the argument for that has been presented above. Adding additional, irrelevant arguments will confuse the Examiner instead of helping prosecution. The specification teaches that compounds of all disclosed formulae (a)-(h) can prevent cardiac arrhythmias and more. Paragraph [0019] of the specification as filed states

> In still another aspect, the present invention provides a method for limiting or preventing a decrease in the level of RyR2-bound FKBP12.6 in a subject, by administering a 1,4-benzothiazepine derivative to the subject, in an amount effective to limit or prevent a decrease in the level of RyR2-bound FKBP12.6 in the subject, wherein the 1,4-benzothiazepine derivative is selected from the group consisting of: [compounds of formulae (a)-(h)].

Formulae (a)-(h) encompass the claimed genera and species. Paragraph [0020] as filed similarly supports the use of the disclosed compounds for "treating or preventing" illustrative cardiac conditions. Thus, the specification clearly teaches that compounds of the claimed genera are capable of performing the claimed methods, not just Compound S36. Applicants respectfully note that actual reduction to practice is not required for patentability. See *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987) ("An applicant need not have actually reduced the invention to practice prior to filing."); *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (C.C.P.A. 1970) ("The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation."); MPEP § 2164.02.

The illustrative cardiac conditions recited in claim 30 are associated with a decreased level of FKBP12.6 binding to RyR2. Compound S36 causes increased binding of FKBP12.6 to RyR2 and is an example of the compounds encompassed in claims 29, 30, 33-34, 43 and 53-58 (which recite genera or subgenera, many of which are the compounds tested in the specification and Appendix B). Since the cardiac conditions recited in claim 30 have a decreased level of FKBP12.6 binding to RyR2, and the illustrative compound S36 increases FKBP12.6 binding to RyR2 and prevents illustrative cardiac arrhythmias, the compounds recited in claims 29, 30, 33-34, 43 and 53-58 are also enabled for treating cardiac arrhythmia. Accordingly, Applicants believe that claims 29, 30, 33-34, 43 and 53-58 are also allowable.

The Office Action cites two articles as raising doubts about this correlation and whether the teachings and the experimental results in the specification are predictive of results in all subjects. However, Applicants believe that these articles do not place doubt on the correlation between Applicant's teachings and experimental data and the expected results in a subject.

The Office Action states at page 5, "The FKBP+/- mice model…fails to provide adequate predictability for all mammals." In support of this statement, the Office Action cites Xin, et al.,

"Oestrogen protects FKBP12.6 null mice from cardiac hypertrophy," *Nature*, March 21, 2002, 416: 334-337 ("Xin"), and Loughrey, et al., "K201 modulates excitation-contraction coupling and spontaneous Ca^{2+} release in normal adult rabbit ventricular cardiomyocytes," *Cardiovascular Research*, 2007, 76:236-246 ("Loughrey"). However, neither reference diminishes the predictability of the FKBP+/- mouse model used in the instant application.

The Office Action states that Xin teaches that "FKBP12.6 knockout mice develop hypertensive cardiac hypertrophy in a sex-specific manner," (see Xin, right column, page 336) and concludes that the FKBP12.6+/- mice model of the present invention is not predictive for both sexes. However, this model (a double knockout model: FKBP12.6-/-) is not relevant to the claimed invention because the model is missing FKBP12.6 altogether, the protein which exhibits increased binding to RyR upon administration of the compounds of the invention. In contrast to Xin, the mouse and rat models in the present application focus on reduced FKBP12.6 expression in heterozygous FKBP+/- mice, in comparison to homozygous FKBP12.6 mice controls used by Xin. See Table 1, Examples 7, 14, and 15. Therefore, the Xin et al. model is not relevant to the claims.

Furthermore, in the abstract, Xin states that disruption of the FKBP12.6 gene in male *and* female mice actually results in *similar* dysregulation of Ca^{2+} release.[1] The authors state that the correlation between the lack of FKBP12.6 binding to RyR and Ca^{2+} overload exists in *both* male and female mice,[2] although the processes by which sex hormones modulate these effects require further study.[3] The Xin et al paper also reported that male FKBP12.6 deficient mice had severe hypertension. This finding likely has nothing to do with the ryanodine receptor but specifically with the deficiency of FKBP12.6 and its effects on the ryanodine receptor (RyR2). Marks, et al., used an independently established FKBP12.6 deficient mouse line in their studies which did not exhibit hypertensive cardiomyopathy in males or females. Thus, the Xin model was possibly a strain specific effect.

The Office Action also relies upon Loughrey et al. and states that Loughrey teaches that

---

1 See Abstract; "[E]quivalent dysregulation of Ca^{2+} release was observed in male and female FKBP12.6$^{-/-}$ mice, but only male mice developed enlarged hearts …" (Xin, left column, 1st full paragraph, p. 335); "Deletion of the *FKBP12.6* gene produces an increase in Ca^{2+} spark duration and an increase in CICR gain, resulting in an increased Ca^{2+} load in both male and female cardiac ventricular myocytes" (Xin, right column, 2nd paragraph, p. 336).
2 "The increase in CICR gain was not significantly different between male and female mice" (Xin, right column, 1st paragraph, p. 334).
3 see Xin, right column, page 336.

JTV-519 (K201) is "ineffective on hearts from FKBP12.6 knockout mice, but effective on rabbits for some of the instantly claimed heart conditions," at page 245, under heading 4.5. However, as with Xin, this statement refers to FKBP12.6 knockout mice (a model which JTV-519 is not expected to work on since JTV acts by restoring binding of FKBP12.6 to RyR2). Applicants believe that their compounds work by stabilizing or increasing the binding of FKBP12.6 to RyR2. Viewing the above sentence in context is also helpful:

> Furthermore, K201 was ineffective on hearts from FKBP12.6 knockout mice. Taken together, the data indicated that K201 acts by restoring FKBP12.6/RyR2 interaction thereby reducing the sensitivity of RyR2 to Ca^{2+}.

(emphasis added). Thus, Loughrey also provides no reason to doubt the predictability of the FKBP12.6+/- mouse model used in the present application, nor does it affect the patentability of the pending claims.

In light of the above, neither Xin nor Loughrey call into question the predictability of the *in vivo* models used in the instant application, either for gender or for the treatment of other mammals. In fact, the *in vitro* and *in vivo* assays in the specification and the cited articles provide evidence that the compounds of the invention are useful for preventing cardiac arrhythmias in several illustrative mammals, including mice, rats, dogs, and humans, and thereby establish the predictability of the models used in the instant specification for mammals. See Examples 1-8 and 12-15.

Moreover, Marks and colleagues have shown that FKBP12.6 deficient mice exhibit exercise induced ventricular arrhythmias and sudden cardiac death, thus supporting their use as a model for these diseases. See Wehrens, et al., Cell 113:829-840, (2003) ("Wehrens").[4] In Wehrens, Marks and colleagues showed that FKBP12.6-deficient mice of both genders exhibit exercise-induced sudden cardiac death due to polymorphic ventricular tachycardia, and that this cardiac death is similar to that manifested by patients with CPVT-linked mutations in RyR2, which causes exercise-induced sudden cardiac death. In FKBP12.6-deficient mice, decreased FKBP12.6 (calstabin2) binding to RyR2 resulted in leaky RyR2 channels. The authors conclude that the Sarcoplasmic Reticulum (SR) Ca^{2+} leak, caused by FKBP12.6-deficient RyR2, triggers fatal cardiac arrhythmias. In addition, in Wehrens, et al., Science 304:292-6, 2004, Marks and

4 "Taken together, these data suggest that the mechanisms for triggered arrhythmias in heart failure patients may be

colleagues showed that by increasing the affinity of FKBP12.6 for RyR2 channels stabilized the closed state of RyR2 and thereby reducing the leak in RyR2 channels, they could prevent the Ca^{2+} leak that triggers exercise-induced, fatal cardiac arrhythmias. Since the recited cardiac conditions result from decreased binding of FKBP12.6 to RyR and can be treated by increasing binding of FKBP12.6 to RyR, a person skilled in the art will be able to use the claimed methods without undue experimentation.

The Office Action states that there is no evidence that would lead one skilled in the art to agree with the assertion that S36 has improved properties relative to JTV-519. Applicants note that the specification states:

> The inventors' novel 1,4-benzothiazepine compounds share functional characteristics with JTV-519. For example, like JTV-519 (mwt=423), compound S36 (mwt=267) regulates calcium channels. Indeed, S36 (a carboxylic acid) is approximately 10 times more potent than JTV-519 in regulating calcium channels (data not shown). Unlike JTV-519, however, the inventors' novel compounds show weak blocking activity of hERGs.

Page 63, lines 10-14. The specification further states:

> Based upon the foregoing, the inventors' novel 1,4-benzothiazepine compounds are more potent than JTV-519, and have reduced toxicity.

Page 63, lines 26-27. As stated in *In re Marzocchi*, Applicant's statements must be taken to be in compliance with the enablement requirement of 35 U.S.C. § 112 unless there is reason to doubt their objective truth. *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367 (C.C.P.A. 1971). In light of the above, Applicants believe that neither the Office Action, Xin nor Loughrey provide reason to doubt the objective truth of the specification.

In light of the above, Applicants request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 112, first paragraph.

Rejections Under 35 U.S.C. § 112 Second Paragraph

Claims 13, 15, 17, 18, 25, 26, 29, 30, 33-35, and 43 have been rejected under 35 U.S.C. §

---

similar to those in CPVT and in the FKBP12.6$^{-/-}$ mouse." Wehrens, p. 838, right column, last full paragraph.

112, second paragraph, as being allegedly indefinite for reciting "or is any oxidized form thereof." Solely to expedite prosecution, claims 13 and 29 have been amended to delete the language, "or is any oxidized form thereof," as Applicants believe that the language would be understood by a person of skill in the art. Claims 15, 17, 18, 25, 26, 29, 30, 33-35, and 43 depend from claim 13 or claim 29. Furthermore, none of new claims 47-69 recite the language, "or is any oxidized form thereof." Thus, applicants believe the rejection has been overcome.

Claim 17 has also been rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for reciting "a candidate for." Claim 17 has been amended to delete "or is a candidate for." Furthermore, none of new claims 47-80 recite, "or is a candidate for." Thus, applicants believe the rejection has been overcome.

Claim 18 has also been rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for reciting "the cardiac condition in the subject" in part (e). Claim 18 has been amended to delete parts (d) and (e), including the language, "the cardiac condition in the subject." Thus, applicants believe the rejection has been overcome.

In view of the above, applicants believe that the presently pending claims meet the requirements of 35 U.S.C. § 112, second paragraph, and respectfully request that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

Nonstatutory Double Patenting

Claims 13, 15, 17, 18, 25, 26, 29, 30, 33-35, and 43 are provisionally rejected on the ground of nonstatutory double patenting over claims 85-106 of copending U.S. Application No. 11/212,309; claims 85-106 of copending U.S. Application No. 11/212,413; and claims 22-31 of copending U.S. Application No. 11/506,285. In reply, applicants submit that this rejection should be withdrawn upon allowance of the claims since the co-pending applications have not yet been patented and the present claims are in condition for allowance. Applicants agree to submit a terminal disclaimer if any of the co-pending applications are allowed or patented prior to the allowance of the present application. If this does not occur, this application should be allowed and these provisional rejections transferred to the other cited applications.

In view of the above, applicants believe that the application is in condition for allowance. Please contact the undersigned if any questions remain.

Please charge any deficiencies in the fees paid for this application, and credit any overpayments to Deposit Account No. 08-0219.

Respectfully submitted,

Date: May 21, 2008

/Jane M. Love, Ph.D./
Jane M. Love, Ph.D.
Reg. No. 42,812

Wilmer Cutler Pickering Hale and Dorr, LLP
399 Park Avenue
New York, New York 10022
Tel: (212) 937-7233
Fax: (212) 230-8888
jane.love@wilmerhale.com